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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/20/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,581	KEEFE ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-21 and 77-100* is/are pending in the application.

4a) Of the above claim(s) *97-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-21 and 77-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's affirmance of the election without traverse of Group I is acknowledged.

Claim Interpretation

2. In claim 1, the phrase "mutated polymerase" is used. However, there is no particular structure assigned in claim 1 to the mutated polymerase. In fact, the term "mutated" simply implies that the polymerase is changed relative to another polymerase sequence. Without any identification of the specific mutations involved, this limitation has two issues. First, there is the issue of written description, as discussed more fully in that rejection. Second, the claim is interpreted broadly as reading on any polymerase, since any polymerase may be interpreted as "mutated" relative to some other polymerase.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 5, 9-11, 17, 19-22, 77 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Pieken et al (U.S. Patent 5,660,985).

Pieken teaches a method of claim 1 for identifying nucleic acid ligands that bind to a target molecule (see abstract) wherein the nucleic acid ligands comprise a 2'-OMe

modified nucleotide (see claim 1 and claim 10, where 2' methoxy groups are expressly claimed),

(a) preparing a transcription mixture comprising a polymerase, modified dNTPs, wherein at least one NTP is 2' OMe NTP and at least one NTP is 2'-OH guanosine triphosphate, magnesium and oligonucleotide transcription templates (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used and see claim 10, which requires the use of a 2' OMe NTP),

(b) preparing a candidate mixture of single-stranded nucleic acids by transcribing the one or more oligonucleotide transcription templates under conditions whereby the polymerase incorporates at least one of the one or more 2' O-methyl modified NTPs into nucleic acid molecules of said candidate mixture (see column 16, lines 13-35, where the T7 RNA polymerase is used to incorporate the NTPs and see claim 10, where the modified nucleotides are 2' O-methyl modified NTPs),

(c) contacting the candidate mixture with said target molecule (see column 16, example 3, lines 13-35 and claim 1),

(d) partitioning the nucleic acids having an increased affinity to the target molecule relative to the candidate mixture from the remainder of the candidate mixture (see column 16, example 3, lines 13-35 and claim 1),

(e) amplifying the increased affinity nucleic acids, in vitro, to yield a ligand enriched mixture of nucleic acids, whereby nucleic acid ligands of the target molecule are identified (see column 16, example 3, lines 13-35 and claim 1).

With regard to claim 5, Pieken teaches T7 RNA polymerase (see column 8, line 24).

With regard to claims 9-11, Pieken teaches a purine leader sequence which is 6 nucleotides in length (see SEQ ID NO: 3).

With regard to claim 17, Pieken teaches the use of 2' OH-guanosine (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used).

With regard to claims 19-20, Pieken teaches the use of PEG (see column 15, line 49).

With regard to claim 21, Pieken teaches repeating the claim steps (see claim 1).

With regard to claim 77, Pieken teaches a variety of ratios of modified to unmodified nucleotides (see column 13, lines 5-7).

With regard to claim 78, Pieken teaches double stranded transcription templates (see column 16, line 11).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pieken et al (U.S. Patent 5,660,985) in view of Brieba et al (Biochemistry (2000) 39:919-923).

Pieken teaches a method of claim 1 for identifying nucleic acid ligands that bind to a target molecule (see abstract) wherein the nucleic acid ligands comprise a 2'-OMe modified nucleotide (see claim 1 and claim 10, where 2' methoxy groups are expressly claimed),

(a) preparing a transcription mixture comprising a polymerase, modified dNTPs, wherein at least one NTP is 2' OMe NTP and at least one NTP is 2'-OH guanosine triphosphate, magnesium and oligonucleotide transcription templates (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used and see claim 10, which requires the use of a 2' OMe NTP),

(b) preparing a candidate mixture of single-stranded nucleic acids by transcribing the one or more oligonucleotide transcription templates under conditions whereby the polymerase incorporates at least one of the one or more 2' O-methyl modified NTPs into nucleic acid molecules of said candidate mixture (see column 16, lines 13-35, where the

T7 RNA polymerase is used to incorporate the NTPs and see claim 10, where the modified nucleotides are 2' O-methyl modified NTPs),

(c) contacting the candidate mixture with said target molecule (see column 16, example 3, lines 13-35 and claim 1),

(d) partitioning the nucleic acids having an increased affinity to the target molecule relative to the candidate mixture from the remainder of the candidate mixture (see column 16, example 3, lines 13-35 and claim 1),

(e) amplifying the increased affinity nucleic acids, in vitro, to yield a ligand enriched mixture of nucleic acids, whereby nucleic acid ligands of the target molecule are identified (see column 16, example 3, lines 13-35 and claim 1).

Pieken does not teach the use of Y639F or H784A T7 RNA polymerase.

Brieba teaches that T7 polymerase mutants at position 784 preferentially utilize 2'-OH groups (see abstract) and position 639 mutants rapidly incorporate 2' modified nucleotides (see page 920).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the T7 RNA polymerase mutants of Brieba in the method of Pieken since Brieba notes that the polymerase with the double mutant is more likely to incorporate 2' substituents (see abstract) and since Pieken would be

motivated by this teaching to utilize polymerases with superior properties for incorporation of the desired 2' modified nucleotides.

8. Claims 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pieken et al (U.S. Patent 5,660,985) in view of Sousa et al (U.S. Patent 6,107,037).

Pieken teaches the limitations of claims 1, 5, 9-11, 17, 19-22, 77 and 78 as discussed above.

Pieken does not teach the use of manganese.

Sousa teaches the use of manganese and magnesium (see column 15, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the magnesium/manganese buffers of Sousa in the method of Pieken since Sousa teaches regarding the use of manganese that "In Mn buffer both the w.t. enzyme and Y639F show a reduction in their sensitivity to substitution of dNTPs for rNTPs, consistent with an expectation of reduced substrate discrimination in Mn buffer. (see column 22, lines 34-37)." An ordinary practitioner would have been motivated to use manganese buffer in optimized concentrations in order to permit incorporation of the modified nucleotides expressly desired by Pieken. Further, an ordinary practitioner would have recognized that the results optimizable variable of Mn concentration could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is

> not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific Manganese concentrations was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

9. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pieken et al (U.S. Patent 5,660,985) in view of Milligan et al (Methods Enzymol. (1989) 180:51-62).

Pieken teaches the limitations of claims 1, 5, 9-11, 17, 19-22, 77 and 78 as discussed above.

Pieken does not teach the use of GMP in T7 RNA polymerase reactions.

Milligan teaches that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use GMP as taught by Milligan when performing the SELEX method of Pieken using modified GTP such as 2'-O methyl GTP since Milligan states that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)." An ordinary practitioner would have been motivated to add GMP whenever low GTP amounts or modified GTP

is being used in transcription reactions, in order to ensure the ability of the T7 RNA polymerase enzyme to prime the extension reaction.

10. Claims 79-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pieken et al (U.S. Patent 5,660,985) in view of Sousa et al (U.S. Patent 6,107,037) and further in view of Milligan et al (Methods Enzymol. (1989) 180:51-62).

Pieken in view of Sousa teach the method of claim 1 and the use of manganese as discussed above.

With regard to claims 81, 82, 90, 91, Pieken teaches a purine leader sequence which is 6 nucleotides in length (see SEQ ID NO: 3).

With regard to claims 83, 92, Pieken teaches a variety of ratios of modified to unmodified nucleotides (see column 13, lines 5-7).

With regard to claims 84, 93, Pieken teaches the use of spermidine (see column 15, line 48).

With regard to claims 85, 94, Pieken teaches the use of PEG (see column 15, line 49).

With regard to claims 86, 95, Pieken teaches double stranded transcription templates (see column 16, line 11).

With regard to claims 87, 96, Pieken teaches repeating the claim steps (see claim 1).

With regard to claim 88, Sousa teaches the use of manganese and magnesium (see column 15, lines 44-48).

Pieken in view of Sousa do not teach the use of GMP as per claims 80 and 89. Milligan teaches that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use GMP as taught by Milligan when performing the SELEX method of Pieken using modified GTP such as 2'-O methyl GTP since Milligan states that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)." An ordinary practitioner would have been motivated to add GMP whenever low GTP amounts or modified GTP is being used in transcription reactions, in order to ensure the ability of the T7 RNA polymerase enzyme to prime the extension reaction.

Response to Arguments

11. Applicant's arguments filed November 22, 2006 have been fully considered but they are not persuasive.

Applicant argues that the term "mutated polymerase" would be understood that the polymerase is mutated relative to wild type. This argument is not persuasive because it is arbitrary what is "wild type" and what is "mutated". This is not solely the opinion of the examiner. For example, Gary Roberts, at http://www.bact.wisc.edu/Bact370/geneticterms.html, states "A change in genotype refers to any known alterations in the DNA sequence from that which is arbitrarily referred to as wild type ("arbitrary" as it is whatever happened to be in the strain

originally isolated from nature)." In concord with this is the question posed at http://www.hgvs.org/mutnomen/refseq.html "Making a judgment on what is the "wild type" (wt) nucleotide for some sequences seems arbitrary at best. How would you suggest that the description be presented for these ?" These citations recognize the common understanding that the term "wildtype" is arbitrary. Therefore, when Applicant uses this term, without definition, in the claims, the broadest reasonable interpretation is that any sequence may be "mutated" relative to some other arbitrarily chosen "wild type" sequence.

Following the arbitrary nature of the term "mutated polymerase" and using the broadest reasonable interpretation, Pieken remains properly anticipatory. This situation is similar to the situation that the Federal Circuit discussed in In re Morris, where the Federal Circuit noted "Absent an express definition in their specification, the fact that appellants can point to definitions or usages that conform to their interpretation does not make the PTO's definition unreasonable when the PTO can point to other sources that support its interpretation." In re Morris, 44 USPQ2d 1023, 1029 (Fed. Cir. 1997). In the current case, there is no limiting language in the specification. Thus, interpreting the polymerase of Pieken as "mutated" is reasonable and comports with the specification which does not define what is the "wild type" polymerase. The Pieken polymerase would be deemed heavily mutated relative to the Adenoviral DNA polymerase or even the T5 RNA polymerase. The decision of the court in In re Bigio, 72 USPQ2d 1209 (Fed. Cir. 2004) strongly supports the breadth of interpretation. That court notes "Nevertheless, this court counsels the PTO to avoid the temptation to limit broad claim

terms solely on the basis of specification passages."

In concert with Morris and Bigio is the decision in In re American Academy of Science Tech Center, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004), where the Federal Circuit noted "We have cautioned against reading limitations into a claim from the preferred embodiment described in the specification, even if it is the only embodiment described, absent clear disclaimer in the specification." Applicant would like to constrain the claim to the preferred embodiment, which is not found in the claims. Based upon Bigio and In re American Academy of Science Tech Center, and the 1997 Morris decision, the Federal Circuit is quite clear that absent a clear disclaimer, which is not present in this case, the broadest reasonable interpretation should be applied to the claims.

Applicant then argues the 103 rejection by stating that Brieba teaches away because the mutation may reduce the polymerase activity. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Brieba taught that the T7 polymerase would be reduced by the mutation, Brieba was not teaching away. Brieba expressly teaches that the mutations at positions 784 and 639 cause a relaxation of specificity for ribose 2' groups (see abstract). The fact that the enzyme was slightly reduced in one

aspect is overcome by the significant improvement in the ability to utilize alternate modified groups.

Pieken is strongly interested in incorporation of modified groups with 2' OH and 2' O-methyl substituents. So when Applicant argues that there is no motivation to use the polymerases of Brieba because of the ranking of the double mutant, this would actually support the motivation to use the H784 mutation which has the same ranking order as the wildtype. However, the ranking is not the whole story, and Applicant's skillful argument evades the central issue, which is the overall increased ability of the mutated polymerases to utilize modified nucleotides. A simple review of figure 2 of Brieba demonstrates that the 639 mutant incorporates significantly more of all of the 2' modified groups than wildtype, which is the precise motivation to use this polymerase. Even if the "rank order" is different, if the amount of even the least well incorporated nucleotide is better than any wildtype incorporation, this provides clear and direct motivation to select this mutant polymerase. Figure 2 also shows that the double mutation has roughly equal incorporation of rATP and superior incorporation of the dATP, 2' F and 2' NH2 groups relative to wildtype. Thus, irrespective of the "preference", the data shows that there is reduced selectivity for ALL 2' nucleotides, which would motivate the ordinary practitioner to use this in the method of Pieken, where alternate 2' nucleotides are utilized.

With regard to the issue of using Manganese, Sousa teaches that Manganese will function. Applicant has not shown any unexpected result from the use of

Manganese and it is a known equivalent of magnesium. Thus, the attorney argument does not represent evidence that it is unexpected to use the known equivalent.

The remaining arguments are repetitive of arguments already addressed above. For these reasons, the rejections will be maintained.

Conclusion

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
1/4/05